

Doc Code: AP.PRE.REQ

PTO/SB/33 (07-05)

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
20781-703

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Signature

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name

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Application Number
09/870,358

Filed
May 30, 2001

First Named Inventor
Chong Jin Oon

Art Unit
1634

Examiner
Jeanine A. Goldberg

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.

See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96)

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January 4, 2006

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

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U.S. APPLICATION SERIAL NO. 09/870,358

REASONS FOR REQUEST FOR REVIEW

This Pre-Appeal Brief Request for Review is submitted in response to the Examiner's Final Office Action mailed August 5, 2005. Claims 22, 26, 27 and 43-46 are pending.

Independent claim 22 is subject to a single rejection, as allegedly unpatentable under 35 U.S.C. §103(a) over Weinberger et al. ("Weinberger") in view of Mbayed et al. ("Mbayed") and further in view of either Ho et al. ("Ho") or Oon et al. ("Oon"). Applicants respectfully traverse the Examiner's rejection based on the following clear errors in the Examiner's rejection of claim 22.

The Examiner has not established a prima facie case of obviousness. To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) teach or suggest **all** the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The claimed invention provides a method for evaluating whether a sample contains HBV that may have escaped immunological detection of HBV surface antigen (HBsAg) by mixing the sample with a set of first and second primers **consisting of** SEQ ID NO: 1 and SEQ ID NO: 2, respectively; performing PCR on the mixture to generate an amplified primer extension product; determining whether the amplified product comprises nucleic acid encoding major HBV surface antigen (SHBsAg) having a mutation at amino acid position 130, from glycine to aspartic acid, or at amino acid position 131 from threonine to asparagine; and identifying the mutation, indicating that the sample contains HBV that may have escaped immunological detection of HBsAg.

Hence, the references, when combined, must teach one of skill in the art to use

- Primers specifically of SEQ ID NO: 1 and SEQ ID NO: 2 to
- Detect and identify mutations that have escaped immunological detection, in particular 130 Gly-Asp, or 131 Thr-Asn.

Applicants respectfully suggest that the references do not do so, and that a prima facie case of obviousness has therefore not been established.

The references at issue are Weinberger and Mbayed. The further references of Ho and/or Oon are relied on by the Examiner to suggest specific mutations of the claim. For purposes of clarity and brevity, Ho and Oon will not be discussed.

As an initial matter, it is not disputed that the references, alone or in combination, do **not** teach the specific primers of the claimed invention. The Examiner has conceded that “Weinberger does not specifically teach using primers of SEQ ID NO: 1 and 2.” (Paper 00805, i.e., Office Action of August 5, 2004, page 4, first full paragraph) and that the primers taught in Mbayed (HBS1 and HBS2) are also not the same as the claimed primers: “SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an additional T nucleotide on the 3’ end. HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application, namely four nucleotides downstream at 694-713.” (Paper 00805, page 4, second full paragraph).

The argument of the Examiner appears to be that, nonetheless, taken together, Weinberger and Mbayed suggest the specific primers of the claimed invention. There are two possibilities for such an argument: 1) the skilled artisan, having the primers of Weinberger, would be led to the primers of the invention because of the suggestions and primers of Mbayed; or 2) the skilled artisan, having the primers of Mbayed, would be led to the primers of the invention because of the suggestions and primers of Weinberger. Although the Examiner is arguing possibility 1) (the claimed invention is unpatentable over Weinberger in view of Mbayed), neither possibility is valid.

1) The skilled artisan, having the primers of Weinberger, would **not** have been led to the primers of the invention because of the suggestions and primers of Mbayed

Specifically, the Examiner argues that “selected SEQ ID NO: 1 and 2 was to area of conserved region and selection was routine.” (Summary of Interview of October 25, 2005, Paper 1005). Starting with Weinberger, the Examiner states, “Primer sequences, which represent highly conserved regions of the s-gene (Table 1) were added to the template DNA.” (Paper 00805, page 4). However, as stated above, the Examiner then concedes that these are not the primers of the claimed invention. Mbayed is then introduced to more closely zero in on the claimed primers: “[T]ordinary artisan would have recognized alternative primers which are also within conserved regions of the HBV nucleic acids would be equivalents to the HBS1 and HBS2 primers [of Mbayed].” (Paper 00805, page 6).

The problem with this approach is that the primers described in Mbayed are described for a completely different purpose than Weinberger, and one of skill in the art, knowing the descriptions of Mbayed and Weinberger, would be no more likely to be led to primers in the vicinity of Mbayed—which still are not the primers of the claimed invention—than to any other primers.

Weinberger and Mbayed are directed at entirely different purposes, and one of skill in the art would not have combined them and then further started looking for yet other primers in order to stumble on the claimed primers. Weinberger describes studies designed to examine the hypothesis that “mutations in the HBsAg itself and especially in its “a” determinant . . . may render the particles undetectable by conventional

immunological assays.” (Weinberger, p. 138, column 2). Weinberger is apparently cited as the closest art in the field of distinguishing mutations that have escaped immunological detection, to which the present claim 22 is directed (i.e., the claim recites “A method for evaluating whether a sample contains HBV that may have escaped immunological detection of HBV surface antigen (HBsAg) the sample contains HBV that may have escaped immunological detection of HBsAg.”). Mbayed, which describes primers closer to the primers of the invention than Weinberger, is directed to the purpose of phylogenetic analysis: the comparison of HBV sequences from different geographic regions in order to “determine the molecular epidemiology of HBV in the pediatric population.” Mbayed, p. 3362, first column; see also phylogenetic tree depicted in Fig. 2 of Mbayed.

These purposes are not compatible, and are not combinable. To distinguish mutations that have escaped immunological detection, as in Weinberger, one needs a set of primers that will reliably and sensitively do so, and it is logical to choose a pair of primers with greatest practical sensitivity among those tested. On the other hand, to perform phylogenetic analysis, as in Mbayed, one needs to use the same set of primers from sample to sample. Phylogenetic analysis is not aimed at detection of new mutations, or even at improved detection of known mutations. Rather, it is directed to comparison of different populations, which requires that samples from different populations be treated, as much as possible, in precisely the same manner—i.e., as much as possible, samples taken in the same manner with the same preservatives, analyzed in the same buffer, at the same temperatures for PCR cycling, with the same enzymes and instrumentation, in the same ionic environment, and, of course, with the same set of primers. Mbayed, in and of itself, teaches **away** from using any other primers than those explicitly described in Mbayed and, as conceded by the Examiner, these are not the primers of the invention.

Thus, one of skill in the art, knowing the descriptions of Weinberger and Mbayed, would be no closer to the primers of the invention than if they had simply read Weinberger—there is nothing in Mbayed to suggest that its primers are preferable or even equivalent to those of Weinberger for finding mutations that have escaped immunological detection, or that there is any reason to think that these primers, or primers near them (as are the primers of the invention), would be any more of a logical starting point for finding such primers than those of Weinberger.

2) The skilled artisan, having the primers of Mbayed, would **not** have been led to the primers of the invention because of the suggestions and primers of Weinberger.

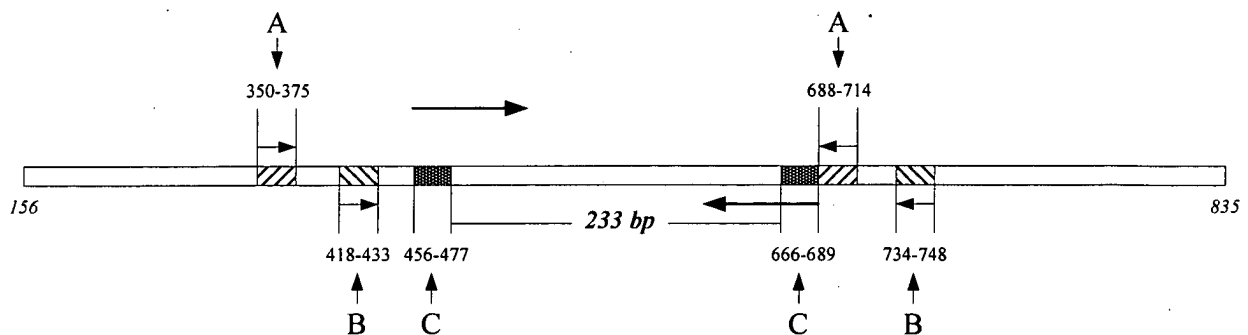
If the skilled artisan started with Mbayed, which describes primers that are closer to the primers of the invention than those of Weinberger, not only would he or she **not** be led to the primers of the invention, he or she would not be led to **any** other primers than those described in Mbayed, because Mbayed is directed to phylogenetic analysis, where the best approach is to use the same of everything in analysis of each sample.

Thus Mbayed teaches away from the primers of the invention and, indeed, from primers that are different in **any** respect from the primers used in Mbayed.

In sum, if the skilled artisan started with Weinberger, as suggested by the Examiner, then Mbayed is not a pointer to the primers of the invention, since Mbayed makes no suggestion or implication that its primers are useful **for the purposes of detecting mutations that have escaped immunological detection**. On the other hand, if the skilled artisan started with Mbayed, which describes primers that are closer to the primers of the invention than those of Weinberger, not only would he or she **not** be led to the primers of the invention, he or she would not be led to **any** other primers than those described in Mbayed, because Mbayed is directed to phylogenetic analysis, where the best approach is to use the same of everything in analysis of each sample.

3) Selection of the primers of the invention was not "routine"

Thus the Examiner is left with Weinberger as the closest art **for the purposes of detecting mutations that have escaped immunological detection**, and the idea that "selection was routine." However, if one of skill in the art and knowledge of Weinberger were to simply select primers, selection is **not** routine. This is demonstrated by the declaration of Dr. Oon of December 25, 2003. This declaration described a comparison of detection of mutations that have escaped immunological detection using either the primers of the invention or other primers known in the art. The primers selected were approximately as close to the primers of the invention as those of Weinberger. For the Panel's convenience and reference, Applicants include a diagram (below) illustrating a comparison of the regions of HBV genome targeted by the different sets of primers from A) Weinberger (chosen from the primers in Table 1 of Weinberger in order to give the forward and reverse primers closest to those of the invention that include the entire region used in the invention); B) The Declaration of Dr. Oon (primers MD14/HD03, described in two papers directed at identifying mutations that have escaped immunological detection: Oon et al. (1995) Vaccine 13:699-702 and Harrison et al. (1991) J. Hepatol. 13: S105-S107); and C) Primer of the Invention (SEQ ID NO: 1 and SEQ ID NO: 2).



Dr. Oon states: "These data show conclusively that the primer pair SEQ ID NO: 1/SEQ ID NO: 2 were superior to the primer pair MD14/HD03. The primer pair MD14/HD03 disclosed in the references were

unable to detect a variety of HBsAg surface mutants. In contrast, the primer pair SEQ ID NO:1/SEQ ID NO:2 were able to detect various HBV Surface antigen negative, but PCR positive HBV viruses, such as the Glycine145Arginine, Glycine130Aspartate, Proline120Serine, and Threonine131Proline mutants.” (Declaration of December 25, 2003, section 9).

The primers of the invention clearly give superior results to other primers in the art that were approximately as close to the primers of the invention as those described in Weinberger. This demonstrates that selection of primers was not merely “routine.”

The Examiner has stated that: “Applicant does not appear to have compared SEQ ID NO: 1 and 2 to the closest prior art, namely, Mbayed.” (Paper 00805, page 10). This is not so—the closest art in the field of the invention, which is **detecting mutations that have escaped immunological detection**, is certainly not Mbayed, which is not directed to this purpose at all, and gives no indication that its primers should or could be used for this purpose. Instead, the declaration is based on the use of primers previously described as useful in detecting variants and especially variants that have escaped immunological detection. See Declaration, page 2, point 5, last sentence. As noted, these primers are as close to the primers of the invention as those of Weinberger (see the diagram above). If Weinberger is not the closest art in the field of detecting mutations that have escaped immunological detection, Applicants respectfully request that the Examiner cite the closest art and drop Weinberger as a reference.

In view of the failure of the cited references to teach or suggest the claimed invention, Applicants submit that a prima facie case of obviousness has not been established under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is respectfully requested. Because all other claims presently under consideration depend from claim 22, and are rejected also only under 35 U.S.C. §103(a), withdrawal of the present rejections of these claims (26, 27, and 43-46) is further respectfully requested.

In light of the remarks set forth above, Applicants believe that they are entitled to a letters patent. Applicants respectfully solicit the Pre-Appeal Conference Panel to expedite the prosecution of this patent application to issuance. Should the Panel have any questions, they are encouraged to telephone the undersigned.